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TOWNSEND and TOWNSEND and CREW LLP

By: /Judith Cotham/

PATENT
Attorney Docket No. 019941-000510US
Client Ref. No. Y0108-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Toyohiro Sawada et al.

Application No.: 09/834,410

Filed: April 12, 2001

For: TIMED-RELEASE COMPRESSION-COATED SOLID COMPOSITION FOR ORAL ADMINISTRATION

Confirmation No. 3651

Examiner: Micah Paul Young

Technology Center/Art Unit: 1618

APPELLANTS' BRIEF UNDER 37 CFR §41.37

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Further to the Notice of Appeal filed on March 31, 2010, for the above-referenced application, Appellants submit this Brief on Appeal. A Petition for a three-month extension of time accompanies this Brief.

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1. REAL PARTY IN INTEREST

The real party in interest is Astellas Pharmaceutical Inc., the assignee of the subject application.

2. RELATED APPEALS AND INTERFERENCES

Notices of Appeal have been filed for this application's continuations, U.S. Patent Application Nos. 11/463,570 (filed December 28, 2006) and 11/841,731 (filed August 21, 2008). An Appeal brief has been filed in U.S. Patent Application No. 11/841,731.

No interferences are pending in related applications.

3. STATUS OF CLAIMS

Claims 1, 3, 5-7, 13-15, 18-21, and 24-36 are pending in this application. Claims 2, 4, 8-12, 16, 17, 22, and 23 have been canceled without prejudice.

Claims 1, 3, 5-7, 13-15, 18-21, and 24-36 are rejected and are appealed.

4. STATUS OF AMENDMENTS

No amendments have been filed since the Final Office Action dated January 4, 2010.

5. SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1

Independent claim 1 sets forth a timed-release compression-coated solid composition for oral administration to a subject, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, wherein said core tablet erodes approximately 40% to approximately 90% in the

digestive tract of said subject, wherein said core tablet does not contain a hydrogel-forming polymer;

i) wherein said drug is metabolized by cytochrome P-450; or

ii) wherein said drug inhibits metabolism by cytochrome P-450; or

iii) wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine;

b) an outer layer, said outer layer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein said hydrogel-forming polymer substance is made from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and said hydrophilic base is polyethylene glycol; and

c) wherein the outer layer does not contain the drug.

Support for most claim elements is found in the original claim as filed (claim 1, page 40, lines 1-6). Support for the claim preamble and the basic tablet structure is also found at page 3, lines 14-21. Support for the list of erodible fillers is found at page 15, lines 6-21. Support for the molecular weight range for the polyethylene glycol filler is found at page 19, lines 15-33, bridging to page 20, lines 1-2, as well as in Exhibits A and B (Official Monographs for Macrogol 400 and Macrogol 200000 submitted with the Appellant's Amendment of August 25, 2009). Support for the rate of tablet erosion is found at page 14, lines 15-31, and in original claim 25. Support for the core's absence of hydrogel is found at pages 23-24 (Examples 1-4) and pages 24-26 (Examples 6-9), wherein the core does not contain a hydrogel. Further support is found at page 17, lines 33-34, bridging to page 18, wherein it states that the hydrogel-forming polymer can also be contained in the core tablet, implying that it may not be contained therein.

Support for the types of drug are found in original claims 16 and 17 as well as the specification at page 5, lines 29-34, bridging to page 6, lines 1-3; and page 11, lines 27-33.

Support for the polyethylene glycol molecular weight range is found at page 17, lines 6-32. Support for lower-molecular-weight polyethylene glycol as the hydrophilic base is found at page 19, lines 15-33, bridging to page 20, lines 1-2.

Support for the outer layer not containing the timed-release drug is found at page 3, lines 14-21.

Independent Claim 21

Independent claim 21 sets forth a method of timed-release of a drug, whereby the composition is orally administered, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, wherein said core tablet erodes approximately 40% to approximately 90% in the digestive tract of said subject, wherein said core tablet does not contain a hydrogel-forming polymer;

i) wherein said drug is metabolized by cytochrome P-450; or

ii) wherein said drug inhibits metabolism by cytochrome P-450; or

iii) wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine;

b) an outer layer, said outer layer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein said hydrogel-forming polymer substance is made from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and said hydrophilic base is polyethylene glycol; and

c) wherein the outer layer does not contain the drug, thereby time releasing the drug.

Support for the method is found in the original claims and the specification at, *e.g.*, Test Example 5. *Id.* at page 31, line 9, bridging to page 33, line 2. Support for the composition's structural elements is found above in the support cited for claim 1.

Dependent Claim 24

Dependent claim 24 sets forth a hydrogel-forming compression-coated solid pharmaceutical preparation comprising: a core tablet containing drug and outer layer made from

hydrogel-forming polymer substance and hydrophilic base, the improvement which comprises a timed-release compression-coated solid composition according to claim 1.

Support for the preparation is found in the original claims and the specification at page 3, lines 22-29. Support for the preparation's additional structural elements is found above in the support cited for claim 1.

Independent Claim 25

Independent claim 25 sets forth a hydrogel-forming compression-coated solid pharmaceutical preparation comprising:

a core tablet containing drug and outer layer made from hydrogel-forming polymer substance and hydrophilic base, the improvement which comprises a timed-release compression-coated solid composition for oral administration, said composition comprising:

(1) a drug and freely erodible filler wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, are mixed with the core tablet, wherein said core tablet does not contain a hydrogel-forming polymer;

a) wherein said drug is metabolized by cytochrome P-450; or

b) wherein said drug inhibits metabolism by cytochrome P-450; or

c) wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine;

(2) the percentage erosion of the core tablet is approximately 40 to approximately 90%; and

(3) the outer layer does not contain the drug and wherein said outer layer is made from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and polyethylene glycol.

Support for the preparation is found in the original claims and the specification at page 3, lines 22-29. Support for the preparation's additional structural elements is found above in the support cited for claim 1.

Dependent Claim 26

Dependent claim 26 sets forth the timed-release compression-coated solid composition for oral administration according to claim 25, wherein the drug is 4'-[(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepin-6-yl)carbonyl]-2-phenylbenzanilide or its salt.

Support for the drug is found in the original claim 20 and the specification at page 14, lines 1-3.

Independent Claim 27

Independent claim 27 sets forth a timed-release compression-coated solid composition for oral administration, to a subject, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, wherein said core tablet does not contain a hydrogel-forming polymer, and wherein said core tablet erodes approximately 40% to approximately 90% in the digestive tract of said subject, wherein percentage erosion is determined by a method wherein said drug is metabolized by cytochrome P-450; or wherein said drug inhibits metabolism by cytochrome P-450; or wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine:

i) a compression-coated tablet is moistened for 3 hours in water at 37° C;

ii) the gelled part of the tablet is peeled off and the portion of the core tablet that has not eroded is removed;

iii) the core tablet is allowed to dry overnight in a dryer at 40° C and the weight is determined;

iv) the value obtained by subtracting dry weight from initial core tablet weight is multiplied by 100;

b) an outer layer, said outer layer is made from a hydrogel-forming polymer substance, and a hydrophilic base, wherein said hydrogel-forming polymer substance is made

from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and said hydrophilic base is polyethylene glycol; and

c) wherein the outer layer does not contain the drug.

Support for the method of determining structural erosion is found at page 14, lines 32-34, bridging to page 15, lines 1-5. Support for the preparation's additional structural elements is found above in the support cited for claim 1.

Dependent Claim 28

Dependent claim 28 sets forth the method of claim 21, wherein interaction is reduced between the drug and a concomitantly used second drug, wherein both drugs employ the same routes for drug absorption.

Support for the claims is found in cancelled claim 22 as well as page 3, lines 30-33, bridging to page 4, lines 1-2 and page 5, lines 8-12; page 31, line 9, bridging to page 33, line 2 (*i.e.*, Test Example 5).

Dependent Claim 29

Dependent claim 29 sets forth the method of claim 28, wherein the drug inhibits drug metabolism *in vivo* in humans of the second drug.

Support for the claims is found in cancelled claim 23 as well as the specification at page 3, lines 30-33, bridging to page 4, lines 1-2 and page 5, lines 8-12.

Independent Claim 30

Independent claim 30 sets forth a timed-release compression-coated solid composition for oral administration to a subject, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, wherein said core tablet erodes approximately 40% to approximately 90% in the digestive tract of said subject, wherein said core tablet contains about 10% to about 50% w/w of a hydrogel-forming polymer;

i) wherein said drug is metabolized by cytochrome P-450; or

ii) wherein said drug inhibits metabolism by cytochrome P-450;or

iii) wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine;

b) an outer layer, said outer layer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein said hydrogel-forming polymer substance is made from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and said hydrophilic base is polyethylene glycol; and

c) wherein the outer layer does not contain the drug.

Support for most of the tablet's structural elements is found above in the support cited for claim 1. Support for about 10% to about 50% of a hydrogel-forming polymer is found in page 17, lines 33-34, bridging to page 18, lines 1-5.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The rejection of claims 1, 3, 5-7, 13-15, 18-21, and 24-36 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 4,925,674 in view of EP 0 661 045 and EP 0 709 386.

In the current Office Action at pg. 5, the Examiner states that Applicant's amendments have been considered and rendered moot in view of a new ground of rejection. However, the rejection purported to be new was *already of record* in the May 27, 2009 Office Action. The rejection is therefore contrary to MPEP § 706.07(a).

7. ARGUMENT

A. The Examiner's Rejection of All Pending Claims under 35 U.S.C. § 103(a)

The Examiner rejected claims 1, 3, 5-7, 13-21 and 24-36 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 4,925,674 ("Giannini") in view of EP 0 661 045 ("Sako") and EP 0 709 386 ("Taniguchi"). The Examiner has asserted that Giannini presents an amoxicillin-containing granule formulation comprising sucrose coated with the drug and a non-hydrogel polymer such as polyvinyl acetate phthalate. Final Rejection of January 4, 2010 ("Final Rejection") 2. This coated core may be further coated with a mixture of ethyl cellulose (*i.e.*, a

hydrogel) and polyethylene glycol (PEG) (*i.e.*, a hydrophilic polymer). *Id.* at 2-3. The Examiner alleges that this structure differs from the claimed invention as to the specific hydrogel polymer, fillers, and drugs, but that these changes would be obvious substitutions from the specific components set forth in the Sako and Taniguchi references. *Id.* at 3, 5.

Appellant will separately argue the patentability of (i) claims 1, 3, 5-7, 13-20, and 27, and 30-36; and (ii) claims 21, 24-26, and 28-29. Appellant respectfully requests that the rejection be reversed and the claims be allowed.

B. The Legal Standard for Obviousness

A claim is obvious when in view of the cited prior art, a claimed invention could have been easily created by an artisan of ordinary skill in the field:

> [T]he differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.
>
> 35 U.S.C. § 103(a).

The factual basis for an obviousness determination is the identification of the relevant prior art, the differences between the prior art and the claimed invention, and the ordinary artisan's level of skill. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). This basis supports or fails to support the legal determination of obviousness, which can be established by various rationales. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). A unifying feature of these rationales is an explicit analysis of the reasons why an invention is obvious:

> The key to supporting any rejection under 35 U.S.C. § 103(a) is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit.
>
> M.P.E.P. § 2143.

Claims 1, 3, 5-7, 13-20, 27, and 30-36

C. The Claim Preamble's Reference to "Timed Release" Is a Claim Limitation.

As an threshold matter, Appellant asserts that the reference to "timed-release" in the preambles of claims 1, 3, 5-7, 13-20, 27, and 30-36 is a claim limitation reciting the feature of timed release.

The standard for evaluating whether a term in a claim's preamble acts as a limitation is whether the preamble was "necessary to give life, meaning, and vitality" to the application's claims. *Kropa v. Robie*, 88 U.S.P.Q. 478, 481 (C.C.P.A. 1951). In *Kropa*, the appellant's initial application did not expressly disclose an "abrasive article," but did teach a combination of various abrasives with a binder resin. *Id.* at 480. Kropa's continuation application claimed an "abrasive brush" comprising abrasive grains and a binder. *Id.* at 479-480. He argued that the combination of elements set forth in the claim was inherently abrasive, so the preamble contained no additional limitation on the claim. *Id.* at 480. The Board refused to allow the priority claim, holding that the property was not inherent to all combinations of abrasives with a binder: "The term calls forth a distinct relationship between the proportions of grain and resin comprising the article." *Id.* at 481.

Similarly here, the claims' preambles set forth a "timed-release" composition. Not all combinations of an inner, drug-containing core with an outer layer of water-soluble PEG and high-molecular-weight PEO would produce timed release. For example, if the outer layer were thin and high in PEG, the outer layer would dissolve very quickly, producing little or no delay before release of the "timed-release" drug from the tablet core. *See* Giannini, Example 8. Timed release compositions are structurally distinct from immediate or even sustained release compositions. They require a distinct relationship between the compositions' outer and inner layers as well as constraints on the structural properties of each layer. Therefore, "timed-release" is a claim limitation.

Furthermore, the specification sets forth a mechanism for how the claimed structure produces timed release, and the claims include its necessary features. *E.g.*, Page 5, lines 1-7. The outer, hydrogel layer absorbs water from the upper digestive tract, forming a gel

surrounding the core. The gel's erosion allows water to penetrate to the core, producing a suspension or solution of the timed-release drug. The gel outer layer is further eroded as it moves through the digestive tract until it disintegrates or peels away to release the timed-release drug mixture and the remaining core tablet in the lower digestive tract. The core's erosion at the time of the drug's release is referenced in claim 1: "wherein said core tablet erodes approximately 40% to approximately 90% in the digestive tract of said subject. . . ." *Id.* at, *e.g.*, page 14, lines 15-34, bridging to page 15, lines 1-5; Claims Appendix at claim 1. Because the preamble's reference to timed release clarifies the purpose and meaning of this core erosion claim limitation, "timed-release" is a claim limitation.

For at least these reasons, the invention as claimed sets forth the element of timed release. Therefore, to support a *prima facie* case of obviousness, the Examiner must show how the combination of cited art teaches the element of timed release. As discussed further below, the Examiner has not shown this.

D. Giannini Teaches Microgranules, Not the Claimed Invention's Tablets.

The combination of art cited by the Examiner does not make the claimed invention obvious because Giannini is directed to a fundamentally different type of composition than the current invention. Giannini sets forth a drug formulation of microgranules usable as a topping for food. Giannini at col. 3, ll. 52-61. The granules are required to be less than 1000 microns (1 mm) in diameter because larger sizes would be inconvenient to administer, difficult to dispense, and gritty to consume. *Id.* at col. 2, ll. 37-55; col. 4, ll. 61-65 and 16-26; col. 6, ll. 55-68. The microgranule taught by Giannini is necessarily much smaller than a tablet for the reasons set forth in the Giannini specification. In contrast, the pending claims are directed to a core tablet comprising an drug, which is covered with an outer, hydrogel layer not containing the drug. Claims Appendix, *e.g.*, claim 1. This outer layer's slow hydration and erosion results in the timed release of drug from the tablet core (see, page 16, lines 24-34, bridging to page 17, line 1; and page 18, lines 6-19). The Examiner's broad description of the Giannini microgranules as a "formulation" obscures the structural gap between Giannini's microcapsules and the claimed invention's tablets. Final Rejection at 2.

Giannini does suggest that the microgranules could be "compressed or formed into a tablet." Giannini at col. 8, ll. 28-33. Such a tablet, however, would still be structurally much different from the instant invention. Because the microgranules described in Giannini are smaller than a tablet, any tablet comprising them would be a conglomerate of many microgranules rather than a single microgranule. This is supported by Giannini's statement that the "microgranules" (*i.e.*, more than one granule) are compressed or formed into a tablet. *Id.* at 30-33. Any prior coating on these microgranules would be dispersed throughout the tablet conglomerate, and Giannini does not teach or suggest an additional outer layer coating the tablet as a whole. *Id.* This differs from the claimed invention's tablet architecture, which includes an outer layer. Claims Appendix at, *e.g.*, claim 1. The tablet's hydration and the slow erosion of the gelled outer layer produces the timed release effect as is currently claimed. Therefore, despite mention of a tablet, Giannini still fails to teach at least this structural element of the claimed invention.

E. Giannini's Coatings Are Designed for Different Functions Than the Present Invention's Timed-Release Outer Layer.

Even if the differences between microgranules and tablets could be ignored, the combination of art cited by the Examiner still does not teach or even suggest all the structural elements necessary to describe the claimed invention. According to the Examiner, Giannini suggests coating the "core tablet" with a mixture of PEG and "oxide." Final Rejection 5. As Giannini's specification only mentions the oxides ethylene oxide and polyethylene oxide, Appellant infers that the Examiner is referring to polyethylene oxide ("PEO"). Giannini's only teaching of PEO, however, is its use as a binder for a drug. Giannini, col. 5, ll. 11-17. The combination of binder and drug forms an active coating around an inert core. *Id.* at ll. 3-5. This differs from the present invention's tablet architecture, in which the outer layer of the tablet does not comprise a timed-release drug of the core. Instead, as is currently taught and claimed, the outer coating layer prevents that drug's release in the upper digestive tract, but the coating slowly absorbs water and degrades as it passes through the digestive tract, allowing that drug's later

release in the lower digestive tract. Claims Appendix, *e.g.*, claims 1, 27, and 30. Thus, the binder coating of Giannini fails to teach or suggest a timed-release outer layer as claimed.

Giannini does teach an optional "taste mask" coating without drug. Giannini at, *e.g.*, Abstract. This taste mask coating can be a mixture of low-molecular-weight PEG and ethyl cellulose. *Id.* at col. 5, ll. 35-44. Even if this coating were interpreted as the outer layer around an active core, it still would not suggest the outer layer as set forth in the claimed invention. Because the taste mask coating only blocks perception of a drug's unpleasant flavor, it has no need to survive more than the few moments that the granules are within a patient's mouth. Giannini demonstrates that the coating did not delay the release of drug by comparing the granules' pharmacokinetic properties with two conventional amoxicillin formulations (Amoxil® suspension and capsules). *Id.* at Example 9. Thus, the taste mask coating of Giannini also fails to teach or suggest a timed-release outer layer as claimed.

Indeed, Giannini teaches away from a timed-release outer layer as claimed because its formulation is explicitly designed for immediate release, and such a layer would prevent immediate release. Giannini at no point describes or suggests a timed- or delayed-release formulation of its drug. Instead, it describes attempts to optimize the taste mask coating to provide faster drug release, optimally within 90 minutes. *Id.* at Example 8; col. 14, lines 17-19. It characterizes exemplary formulations as "immediate release." *Id.* at Examples 7 and 8. In fact, it presents the use of an ethyl cellulose coating allowing immediate release as a point of novelty for its formulation, contrasting this with its more common use in sustained-release applications. *Id.* at col. 13, lines 59-66. Thus, the taste mask coating of Giannini teaches away from a timed-release outer layer as claimed.

F. Giannini's Core Does Not Contain a Drug

Furthermore, Giannini teaches a core of solid sucrose, *i.e.*, an inert sucrose seed. *Id.* at col. 6, lines 27-32, 55-60. The inert sucrose solid seed comprises no drug. Instead, it is coated with an active layer or layers containing amoxicillin and a binder such as hydroxypropyl methyl cellulose (a hydrogel). Giannini at, *e.g.*, 8, line 47, to 9, line 39.

In contrast, the claimed invention's core comprises a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of between 400 to 20,000, sucrose, and lactulose. Claims Appendix at, *e.g.*, claim 1. The claimed invention's core is not inert as it comprises a drug. Thus, Giannini teaches a different structure that may have different properties.

The Examiner has attempted to redefine Giannini's pharmaceutically active coated seed as the as the "core tablet." Final Rejection at 2-3, 5. One of skill in the art, however, would understand that Giannini teaches an inert core that is coated with amoxicillin. Giannini at, *e.g.*, 8, line 47, to 9, line 39. The Examiner has not shown that this different structure would produce the same level of core erosion or produce the same release characteristics as the claimed invention. Thus, Giannini again fails to teach all structural elements of the claimed invention.

G. Sako and Taniguchi Do Not Supply the Missing Claim Elements.

Appellant notes that the Examiner has not attempted to demonstrate how these two references could supply the missing claim elements. Indeed, neither Sako nor Taniguchi can supply the claimed structural elements missing from Giannini. Sako teaches a homogeneous tablet formulation that comprises a drug, a hydrogel-forming polymer, and an additive providing for the penetration of water into the core of the preparation. Sako at, *e.g.*, Abstract. In contrast, the pending claims set forth a heterogeneous tablet comprising an inner core and an outer layer. Claims Appendix at, *e.g.*, claim 1. Sako teaches that the tablet's drug is intermixed with a hydrogel polymer. Sako at 2, lines 41-45; 8, line 42 to 10, line 54. In contrast, the pending claims exclude the tablet core's timed-release drug from the tablet's PEO outer layer. Claims Appendix at, *e.g.*, claim 1. Sako teaches a sustained-release tablet that continuously releases its drug from the upper digestive tract to the colon. Sako at 2, lines 4-6. In contrast, the pending claims set forth a timed-release tablet: The tablet does not release the timed-release drug in the upper digestive tract, but erosion of the tablet's outer layer produces a selective, delayed release in the lower digestive tract. Therefore, Sako also fails to teach or to suggest the outer coating and the timed release set forth in the claimed invention.

Taniguchi teaches benzazepine compounds and pharmaceutical compositions thereof. Taniguchi, Abstract. Taniguchi generally discloses some pharmaceutical ingredients that can be used to formulated a tablet comprising the benzazepine compounds. *Id.* at 27, lines 22-37. Taniguchi also discloses an optional "film of gastric or enteric substance." *Id.* at lines 36-37. Taniguchi provides an example of a tablet coated with hydroxypropyl cellulose and PEG 6000, but does not teach the use of high-molecular-weight PEO for this purpose. *Id.*; *Id.* at 54, lines 5-7. Taniguchi provides no suggestion regarding the claimed invention's specific outer layer or its timed release in the lower intestinal tract. Therefore, Taniguchi also fails to teach or to suggest the outer coating and the timed release set forth in the claimed invention.

H. The Cited Art Provides No Motivation to Combine Elements.

Appellant notes that the Examiner cites Sako and Taniguchi for allegedly providing filler, coating, and drug elements to be substituted into the granule structure set forth in Giannini. Final Rejection at 3, 5. The explicit motivation for this substitution of elements, however, is detailed only in vague terms. *See Id.* For example, although the Examiner asserts that "it would have been obvious" to combine numerous elements from different references to "provide proper release," the Examiner does not specify what is meant by "proper release" or which cited reference teaches timed release as set forth in the pending claims. *Id.* at 5. Appellant does not see how this showing provides a "clear articulation of the reason(s) why the claimed invention would have been obvious." M.P.E.P. § 2143. Therefore, the Examiner has failed to show the explicit motivation necessary to establish a *prima facie* case of obviousness.

Claims 21, 24-26, and 28-29

I. The Claims Recite "Timed Release" as an Express Limitation.

As a threshold matter, Appellant notes that claims 21, 24, 26, and 28-29 include a reference to timed release in their claim preambles. Therefore, for all the reasons set forth above, the claim preamble's recitation of "timed-release" is a limitation.

Even if the claim preambles' reference to timed release were alleged to be a non-limiting purpose or intended use, claims 24-26 set forth a pharmaceutical preparation that includes "the improvement which comprises a timed-release compression-coated solid

composition." Claims Appendix at claims 24-26 (emphasis added). Claims 21 and 28-29 set forth a method of treatment that includes "time releasing the drug." Claims Appendix at claims 21, 28-29 (emphasis added). Because "timed-release compression-coated solid formulation" and "time releasing the drug" are expressly set forth within the body of these claims, these claims are directed to timed-release compositions and methods.

Therefore, to support a *prima facie* case of obviousness, the Examiner must show how the combination of cited art teaches the element of timed release. As discussed above, the Examiner has not shown this.

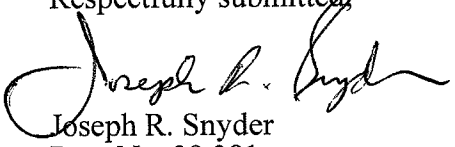
J. The Cited Art Does Not Establish Obviousness under 35 U.S.C. § 103(a).

Appellant incorporates by reference the additional arguments for non-obviousness set forth for claims 1, 3, 5-7, 13-20, 27, and 30-36. Claims 21 and 25 are offered as examples from the second group of claims.

8. CONCLUSION

For these reasons, it is respectfully submitted that the rejection should be reversed for both groups of claims. Accordingly, Applicants respectfully request that the rejection of all claims be withdrawn and that this application be set to issue.

Respectfully submitted,



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9. CLAIMS APPENDIX

1. (Previously Presented) A timed-release compression-coated solid composition for oral administration to a subject, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, wherein said core tablet erodes approximately 40% to approximately 90% in the digestive tract of said subject, wherein said core tablet does not contain a hydrogel-forming polymer;

i) wherein said drug is metabolized by cytochrome P-450; or

ii) wherein said drug inhibits metabolism by cytochrome P-450; or

iii) wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine;

b) an outer layer, said outer layer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein said hydrogel-forming polymer substance is made from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and said hydrophilic base is polyethylene glycol; and

c) wherein the outer layer does not contain the drug.

2. (Canceled)

3. (Original) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein there is approximately 75 wt% or less of said

drug, approximately 5 to approximately 80 wt% freely erodible filler, approximately 10 to approximately 95 wt% hydrogel-forming polymer substance, and approximately 5 to approximately 80 wt% hydrophilic base.

4. (Canceled)

5. (Original) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid.

6. (Original) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the freely erodible filler for a basic drug is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid.

7. (Original) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the freely erodible filler for an acidic or neutral drug is 1 or 2 or more selected from the group consisting of polyethylene glycol, sucrose or lactulose.

8-12. (Canceled)

13. (Original) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the hydrogel-forming polymer substance is at least 1 type of polyethylene oxide and further contains red ferric oxide and/or yellow ferric oxide.

14. (Original) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein a drug is brought to be effectively released or absorbed in the lower digestive tract.

15. (Original) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein a drug is brought to be effective for chronopharmacotherapy.

16-17. (Canceled)

18. (Previously Presented) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the drug is metabolized by CYP3A4.

19. (Previously Presented) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the drug has the effect of inhibiting metabolism by CYP3A4.

20. (Original) The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the drug is 4'-[(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepin-6-yl)carbonyl]-2-phenylbenzanilide or its salt.

21. (Previously Presented) A method of timed-release of a drug, whereby the composition is orally administered, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid,

tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, wherein said core tablet erodes approximately 40% to approximately 90% in the digestive tract of said subject, wherein said core tablet does not contain a hydrogel-forming polymer;

i) wherein said drug is metabolized by cytochrome P-450; or

ii) wherein said drug inhibits metabolism by cytochrome P-450; or

iii) wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine;

b) an outer layer, said outer layer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein said hydrogel-forming polymer substance is made from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and said hydrophilic base is polyethylene glycol; and

c) wherein the outer layer does not contain the drug, thereby time releasing the drug.

22-23. (Canceled)

24. (Original) In a hydrogel-forming compression-coated solid pharmaceutical preparation comprising: a core tablet containing drug and outer layer made from hydrogel-forming polymer substance and hydrophilic base, the improvement which comprises a timed-release compression-coated solid composition according to claim 1.

25. (Previously Presented) A hydrogel-forming compression-coated solid pharmaceutical preparation comprising:

a core tablet containing drug and outer layer made from hydrogel-forming polymer substance and hydrophilic base, the improvement which comprises a timed-release compression-coated solid composition for oral administration, said composition comprising:

(1) a drug and freely erodible filler wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, are mixed with the core tablet, wherein said core tablet does not contain a hydrogel-forming polymer;

a) wherein said drug is metabolized by cytochrome P-450; or

b) wherein said drug inhibits metabolism by cytochrome P-450; or

c) wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine;

(2) the percentage erosion of the core tablet is approximately 40 to approximately 90%; and

(3) the outer layer does not contain the drug and wherein said outer layer is made from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and polyethylene glycol.

26. (Original) The timed-release compression-coated solid composition for oral administration according to claim 25, wherein the drug is 4'-[(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepin-6-yl)carbonyl]-2-phenylbenzanilide or its salt.

27. (Previously Presented) A timed-release compression-coated solid composition for oral administration, to a subject, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, wherein said core tablet does not contain a hydrogel-forming polymer, and wherein said core tablet erodes approximately 40% to approximately 90% in the digestive tract of said subject, wherein percentage erosion is determined by a method wherein said drug is metabolized by cytochrome P-450; or wherein said drug inhibits metabolism by cytochrome P-450; or wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine:

i) a compression-coated tablet is moistened for 3 hours in water at 37° C;

ii) the gelled part of the tablet is peeled off and the portion of the core tablet that has not eroded is removed;

iii) the core tablet is allowed to dry overnight in a dryer at 40° C and the weight is determined;

iv) the value obtained by subtracting dry weight from initial core tablet weight is multiplied by 100;

b) an outer layer, said outer layer is made from a hydrogel-forming polymer substance, and a hydrophilic base, wherein said hydrogel-forming polymer substance is made from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and said hydrophilic base is polyethylene glycol; and

c) wherein the outer layer does not contain the drug.

28. (Previously presented) The method of claim 21, wherein interaction is reduced between the drug and a concomitantly used second drug, wherein both drugs employ the same routes for drug absorption.

29. (Previously presented) The method of claim 28, wherein the drug inhibits drug metabolism *in vivo* in humans of the second drug.

30. (Previously Presented) A timed-release compression-coated solid composition for oral administration to a subject, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of about 400 to 20,000, sucrose, and lactulose, wherein said core tablet erodes approximately 40% to approximately 90% in the digestive tract of said subject, wherein said core tablet contains about 10% to about 50% w/w of a hydrogel-forming polymer;

i) wherein said drug is metabolized by cytochrome P-450; or

ii) wherein said drug inhibits metabolism by cytochrome P-450;or

iii) wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine;

b) an outer layer, said outer layer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein said hydrogel-forming polymer substance is made from at least one type of polyethylene oxide with a viscosity-average molecular weight of 2,000,000 or higher, and said hydrophilic base is polyethylene glycol; and

c) wherein the outer layer does not contain the drug.

31. (Previously presented) The timed-release compression-coated solid composition for oral administration according to claim 30, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid.

32. (Previously presented) The timed-release compression-coated solid composition for oral administration according to claim 30, wherein the freely erodible filler for a basic drug is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid.

33. (Previously presented) The timed-release compression-coated solid composition for oral administration according to claim 30, wherein the freely erodible filler for an acidic or neutral drug is 1 or 2 or more selected from the group consisting of polyethylene glycol, sucrose or lactulose.

34. (Previously presented) The timed-release compression-coated solid composition for oral administration according to claim 30, wherein the hydrogel-forming polymer substance is at least 1 type of polyethylene oxide and further contains red ferric oxide and/or yellow ferric oxide.

35. (Previously presented) The timed-release compression-coated solid composition for oral administration according to claim 30, wherein a drug is brought to be effectively released or absorbed in the lower digestive tract.

36. (Previously presented) The timed-release compression-coated solid composition for oral administration according to claim 30, wherein a drug is brought to be effective for chronopharmacotherapy.

10. EVIDENCE APPENDIX

Exhibit A is the Official Monograph for Macrogol 400. Exhibit A was previously submitted and entered with the Appellant's Amendment of August 25, 2009.

Exhibit B is the Official Monograph for Macrogol 200000. Exhibit B was previously submitted and entered with the Appellant's Amendment of August 25, 2009.

11. RELATED PROCEEDINGS APPENDIX

No decisions have been rendered in related proceedings.

EXHIBIT A

purple color at the outer portion of cortex, and light brown inner portion making irregular wave; xylem yellowish in color; the center of the crown is often cracked, and the surrounding part red-purple. Odor, slight; taste, slightly sweet.

Identification (1) Heat 0.5 g of pulverized Lithospermum Root in a test tube: red vapor evolves, which condenses on the wall of the upper part of the tube into red-brown oil drops.

(2) Shake 0.5 g of pieces or powder of Lithospermum Root with 1 mL of ethanol (95), and to the red solution thereby obtained add 1 drop of sodium hydroxide TS: the red color changes to blue-purple. To this solution add 1 to 2 drops of dilute hydrochloric acid: the color turns red again.

(3) To 0.5 g of pulverized Lithospermum Root add 5 mL of ethanol (95), shake for 30 minutes, filter, and evaporate the filtrate at a temperature not higher than 40°C under reduced pressure. Add 1 mL of ethanol (95) to the residue, and use this solution as the sample solution. Perform the test with this solution as directed under the Thin-layer Chromatography. Spot 5 μL of the sample solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and ethanol (95) (3:1) to a distance of about 10 cm, and air-dry the plate: a red-purple spot appears around the *Rf* 0.75.

Total ash Not more than 11.0%.

Acid-insoluble ash Not more than 3.5%.

Longgu

Fossilia Ossis Mastodi

リュウコツ

Longgu is the ossified bone of large mammal, and is mainly composed of calcium carbonate.

Description Irregular masses or fragments, occasionally cylindrical masses; externally light grayish white, sometimes with grayish black or yellow-brown spots here and there; the outer part consists of a layer 2 – 10 mm in thickness, and is minute in texture, surrounding the light brown, porous portion; heavy and hard, but somewhat fragile in texture; when crushed, it changes into pieces and powder. Odorless, tasteless, and strongly adhesive to the tongue on licking.

Identification (1) Dissolve 0.5 g of pulverized Longgu in 10 mL of dilute hydrochloric acid: it evolves a gas, and forms a slightly brownish and turbid solution. Pass the gas evolved through calcium hydroxide TS: a white precipitate is produced.

(2) The turbid solution, obtained in (1), has a characteristic odor. Filter this solution, and neutralize with ammonia TS: the solution responds to the Qualitative test for calcium salt.

(3) Dissolve 0.1 g of pulverized Longgu in 5 mL of nitric acid by warming, and add hexaammonium heptamolybdate TS: a yellow precipitate is produced.

Purity (1) Heavy metals—To 2.0 g of pulverized Longgu add 5 mL of water, shake to mix, add carefully 6 mL of hydrochloric acid, and evaporate on a water bath to dryness. Dissolve the residue in 50 mL of water, and filter. To 25 mL of the filtrate add 2 mL of dilute acetic acid, 1 drop of ammonia TS and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution as follows: Evaporate 3 mL of hydrochloric acid on a water bath to dryness, add 2 mL of dilute acetic acid and 2.0 mL of Standard Lead Solution, and add water to make 50 mL (not more than 20 ppm).

(2) Arsenic—Prepare the test solution with 0.20 g of pulverized Longgu according to Method 2, and perform the test using Apparatus B (not more than 10 ppm).

Macrogol 400

Polyethylene Glycol 400

マクロゴール 400

Macrogol 400 is a polymer of ethylene oxide and water, represented by the formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, in which the value of n ranges from 7 to 9.

Description Macrogol 400 occurs as a clear, colorless and viscous liquid. It has no odor or a slight, characteristic odor.

It is miscible with water, with methanol, with ethanol (95) and with pyridine.

It is soluble in diethyl ether.

It is slightly hygroscopic.

Congealing point: 4 – 8°C

Specific gravity d_{20}^{20}: 1.110 – 1.140

Identification Dissolve 0.05 g of Macrogol 400 in 5 mL of dilute hydrochloric acid, add 1 mL of barium chloride TS, shake, and filter, if necessary. To the filtrate add 1 mL of a solution of phosphomolybdic acid *n*-hydrate (1 in 10): a yellow-green precipitate is formed.

pH Dissolve 1.0 g of Macrogol 400 in 20 mL of water: the pH of this solution is between 4.0 and 7.0.

Purity (1) Acid—Dissolve 5.0 g of Macrogol 400 in 20 mL of neutralized ethanol, and add 2 drops of phenolphthalein TS and 0.20 mL of 0.1 mol/L sodium hydroxide VS: the solution is red in color.

(2) Ethylene glycol and diethylene glycol—Dissolve 4.0 g of Macrogol 400 in water to make exactly 10 mL, and use this solution as the sample solution. Weigh accurately about 0.05 g each of ethylene glycol and diethylene glycol, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 2 μL each of the sample solution and the standard solution as directed under the Gas Chromatography according to the following conditions. Determine the peak heights, H_{Ta} and H_{Sa}, of ethylene glycol of each solution, and the peak heights, H_{Tb} and H_{Sb}, of diethylene glycol, and calculate the amount of ethylene glycol and diethylene glycol: the sum of the contents of ethylene glycol and diethylene glycol is not more than 0.25%.

Amount (mg) of ethylene glycol
= amount (mg) of ethylene glycol for gas chromatography $\times \frac{H_{Ta}}{H_{Sa}} \times \frac{1}{10}$

Amount (mg) of diethylene glycol
= amount (mg) of diethylene glycol for gas chromatography $\times \frac{H_{Tb}}{H_{Sb}} \times \frac{1}{10}$

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A colum about 3 mm in inside diameter and about 1.5 m in length, packed with siliceous earth for gas chromatography, 150 to 180 μm in particle diameter, coated with D-sorbitol at the ratio of 12%.

Column temperature: A constant temperature of about 165°C.

Carrier gas: Nitrogen or helium.

Flow rate: Adjust the flow rate so that the retention time of diethylene glycol is about 8 minutes.

Selection of column: Proceed with 2 μL of the standard solution under the above operating conditions, and calculate the resolution. Use a column clearly dividing peaks of ethylene glycol and diethylene glycol in this order.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of diethylene glycol obtained from 2 μL of the standard solution composes about 80% of the full scale.

Average molecular mass Add 42 g of phthalic anhydride to 300 mL of freshly distilled pyridine, exactly measured, in a 1-L light-resistant glass-stoppered bottle. Shake the bottle vigorously to dissolved the solid, and allow to stand for 16 hours or more. Pipet 25 mL of this solution into an about 200-mL glass-stoppered pressure bottle. Add about 1.5 g of Macrogol 400, accurately weighed, stopper the bottle, wrap it securely with strong cloth, and immerse in a water bath, having a temperature of 98 ± 2°C, to the level so that the mixture in the bottle soaks completely in water. Maintain the temperature of the bath at 98 ± 2°C for 30 minutes. Remove the bottle from the bath, and allow to cool in air to room temperature. Add exactly 50 mL of 0.5 mol/L sodium hydroxide VS and 5 drops of a solution of phenolphthalein in pyridine (1 in 100). Titrate with 0.5 mol/L sodium hydroxide VS until a light red color remains for not less than 15 seconds. Perform a blank determination.

$$\text{Average molecular mass} = \frac{\text{mass (g) of sample} \times 4000}{a - b}$$

a: Volume (mL) of 0.5 mol/L sodium hydroxide VS used in the blank determination.

b: Volume (mL) of 0.5 mol/L sodium hydroxide VS used in the test of the sample.

Average molecular mass is between 380 and 420.

Water Not more than 1.0% (2 g, direct titration).

Residue on ignition Not more than 0.10% (1 g).

Containers and storage Containers—Tight containers.

Macrogol 1500

Polyethylene Glycol 1500

マクロゴール 1500

Macrogol 1500 is a mixture containing equal amounts of lower and higher polymers of ethylene oxide and water, represented by the formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, in which the value of *n* is 5 or 6 for the lower polymers and from 28 to 36 for the higher.

Description Macrogol 1500 occurs as a white, smooth petrolatum-like solid. It is odorless or has a faint, characteristic odor.

It is very soluble in water, in pyridine and in diphenyl ether, freely soluble in methanol, sparingly soluble in ethanol (95), very slightly soluble in ethanol (99.5), and practically insoluble in diethyl ether.

Congealing point: 37 - 41°C

Identification Dissolve 0.05 g of Macrogol 1500 in 5 mL of dilute hydrochloric acid, add 1 mL of barium chloride TS, shake, and filter, if necessary. To the filtrate add 1 mL of a solution of phosphomolybdic acid *n*-hydrate (1 in 10): a yellow-green precipitate is formed.

pH Dissolve 1.0 g of Macrogol 1500 in 20 mL of water: the pH of the solution is between 4.0 and 7.0.

Purity (1) Clarity and color of solution—Dissolve 5.0 g of Macrogol 1500 in 50 mL of water: the solution is clear and colorless.

(2) Acid—Dissolve 5.0 g of Macrogol 1500 in 20 mL of neutralized ethanol, and add 2 drops of phenolphthalein TS and 0.20 mL of 0.1 mol/L sodium hydroxide VS: the solution is red in color.

(3) Ethylene glycol and diethylene glycol—Place 50.0 g of Macrogol 1500 in a distilling flask, add 75 mL of diphenyl ether, warm to dissolve if necessary, distil slowly under a reduced pressure of 0.13 to 0.27 kPa and take 25 mL of the distillate in a 100-mL container with 1-mL graduation. To the distillate add exactly 20 mL of water, shake vigorously, cool in ice water, congeal the diphenyl ether, and filtrate into a 25-mL volumetric flask. Wash the residue with 5.0 mL of ice-cold water, combine the washings with the filtrate, warm to room temperature, and add water to make 25 mL. Transfer this solution to a glass-stoppered flask, shake with 25.0 mL of freshly distilled acetonitrile, and use this solution as the sample solution. Separately, to 62.5 mg of diethylene glycol add a mixture of water and freshly distilled acetonitrile (1:1) to make exactly 25 mL, and use this solution as the standard solution. Take exactly 10 mL each of the sample solution and the standard solution, and add to each exactly 15 mL of cerium (IV) diammonium nitrate TS. Perform the test with this solution as directed under the Ultraviolet-visible Spectrophotometry within 2 to 5 minutes: the absorbance of the solution obtained from the sample solution at the wavelength of maximum absorption at about 450 nm is not larger than the absorbance of the solution obtained from the standard solution.

Water Not more than 1.0% (2 g, direct titration).

EXHIBIT B

Titrate with 0.5 mol/L sodium hydroxide VS until a light red color remains for not less than 15 seconds. Perform a blank determination in the same manner.

$$\text{Average molecular mass} = \frac{\text{mass (g) of sample} \times 4000}{a - b}$$

a: Volume (mL) of 0.5 mol/L sodium hydroxide VS consumed in the blank determination.
b: Volume (mL) of 0.5 mol/L sodium hydroxide VS consumed in the test of the sample.

Average molecular mass is between 7300 and 9300.

Water Not more than 1.0% (2 g, direct titration).

Residue on ignition Not more than 0.25% (1 g).

Containers and storage Containers—Well-closed containers.

Macrogol 20000

Polyethylene Glycol 20000

マクロゴール 20000

Macrogol 20000 is a polymer of ethylene oxide and water, represented by the formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, in which the value of *n* lies between 340 and 570.

Description Macrogol 20000 occurs as white, paraffin-like flakes or powder. It is ordorless or has a faint, characteristic odor.

It is freely soluble in water and in pyridine, and practically insoluble in methanol, in ethanol (95), in anhydrous diethyl ether, in petroleum benzine and in macrogol 400.

Congealing point: 56 - 64°C

Identification Dissolve 0.05 g of Macrogol 20000 in 5 mL of dilute hydrochloric acid, add 1 mL of barium chloride TS, shake, and filter, if necessary. To the filtrate add 1 mL of a solution of phosphomolybdic acid *n*-hydrate (1 in 10): a yellow-green precipitate is formed.

pH Dissolve 1.0 g of Macrogol 20000 in 20 mL of water: the pH of this solution is between 4.5 and 7.5.

Purity (1) Clarity and color of solution—Dissolve 5.0 g of Macrogol 20000 in 50 mL of water: the solution is clear and colorless.

(2) Acid—Dissolve 5.0 g of Macrogol 20000 in 20 mL of neutralized ethanol by warming, cool, and add 0.20 mL of 0.1 mol/L sodium hydroxide VS and 1 drop of phenolphthalein TS: the color of the solution is red.

Average molecular mass Weigh accurately about 15.0 g of Macrogol 20000, transfer to an about 200-mL glass-stoppered pressure bottle, add about 25 mL of pyridine, dissolve by warming, and allow to cool. Separately, pipet 300 mL of freshly distilled pyridine into a 1000-mL light-resistant glass-stoppered bottle, add 42 g of phthalic anhydride, dissolve with vigorous shaking, and allow to stand for 16 hours or more. Pipet 25 mL of this solution, transfer to the former pressure bottle, stopper the bottle tightly, wrap it securely with strong cloth, and immerse in a water bath, having a temperature of 98 ± 2°C, to the same depth as the mixture in the bottle. Maintain the temperature of the bath at 98 ± 2°C for 60 minutes. Remove the bottle from the bath, and allow to cool in air to room temperature. Add exactly 50 mL of 0.5 mol/L sodium hydroxide VS and 5 drops of a solution of phenolphthalein in pyridine (1 in 100). Titrate with 0.5 mol/L sodium hydroxide VS until a light red color remains for not less than 15 seconds. Perform a blank determination.

$$\text{Average molecular mass} = \frac{\text{mass (g) of sample} \times 4000}{a - b}$$

a: Volume (mL) of 0.5 mol/L sodium hydroxide VS used in the blank determination.
b: Volume (mL) of 0.5 mol/L sodium hydroxide VS used in the test of the sample.

Average molecular mass is between 15000 and 25000.

Water Not more than 1.0% (2 g, direct titration).

Residue on ignition Not more than 0.25% (1 g).

Containers and storage Containers—Well-closed containers.

Macrogol Ointment

Polyethylene Glycol Ointment

マクロゴール軟膏

Method of preparation

Macrogol 4000	500 g
Macrogol 400	500 g
To make	1000 g

Melt Macrogol 4000 and Macrogol 400 by warming on a water bath at 65°C, and mix well until it congeals. Less than 100 g of Macrogol 4000 or Macrogol 400 may be replaced by an equal amount of Macrogol 400 or Macrogol 4000 to prepare 1000 g of a proper soft ointment.

Description Macrogol Ointment is white in color. It has a faint, characteristic odor.

Identification Dissolve 0.05 g of Macrogol Ointment in 5 mL of dilute hydrochloric acid, add 1 mL of barium chloride TS, shake, filter if necessary, and add 1 mL of a solution of phosphomolybdic acid *n*-hydrate (1 in 10) to the filtrate: a yellow-green precipitate is formed.

Containers and storage Containers—Tight containers.